5. Hansen LA, Alexander N, Hogan ME, et al Genetically null mice reveal a central role for epidermal growth factor receptor in the differentiation of the hair follicle and normal hair development. *Am J Pathol* 1997;150:1959–1975.

Reply: Randomized Controlled Trial of Resection Versus Radiotherapy After Induction Chemotherapy in Stage IIIA-N2 Non-Small Cell Lung Cancer

To the Editor:

We recognize the excellent work done by the authors of this editorial in advancing the boundaries of lung cancer surgery.[1] However, the remarkable survival figures they cited were not all based on an intention-to-treat analysis. We also fear that their enthusiasm may blur a rational interpretation of the results of EORTC 08941 for most clinicians who practice outside very specialized tertiary centers.[2]

One of the strengths of EORTC 08941 lies in the fact that study patients represent a fair case mix of patients with clinical stage IIIA-N2 non-small cell lung cancer (NSCLC) who were diagnosed, staged, and treated between 1994 and 2002 in different hospitals throughout Europe. As such, these patients are more representative of the real world than the series cited by the editorial's authors. The conclusions of EORTC 08941 are applicable to these real-world patients and institutions. Extrapolating the results of highly selected series to the community introduces a level of evidence that is inappropriate for a highly prevalent disease such as lung cancer.

The editorialists' arguments that surgery should be offered to patients who are likely to be down-staged, and in whom a complete resection can be obtained with a lobectomy, are of a circular kind. However, inasmuch as these factors are derived from a multivariable analysis, then used to categorize the same data, this is unsurprising. To prove the predictive validity of these factors, they should be applied to a new series, not to the one from which they were derived. More importantly, even if they have been validated as predictive factors associated with survival after surgery, such analysis cannot be used to select those likely to benefit most from surgery because the notion of differential benefit is based entirely on the presumption of efficacy. Another flaw in using these factors to select patients who are most likely to benefit from radical surgery is that they were all defined postoperatively. Completeness of resection can only be defined post hoc, lymph node status is revised as part of pathological staging, and most—if not all—surgeons are not likely to be certain before the operation that a pneumonectomy will definitely not be necessary for an individual patient with IIIA-N2, even in one showing radiological evidence of response. This fact is illustrated by the high rates of pneumonectomy (28–44%) in the series the editorialists quoted, a figure not dissimilar to the rate of 46% observed in EORTC 08941. If we are to have a set of criteria by which to select or counsel patients, these criteria must be available before surgery and be validated before they can be used.

We concur with the editorialists that further research is needed to improve the accuracy of diagnosing mediastinal down-staging by non-surgical techniques such as endoscopic ultrasound and positron emission tomography scan. However, the performance of these techniques should be carefully assessed in randomized trials, as their costs are high and the characteristics of the equipment might differ.

Several uncontrolled series with chemoradiation regimens in stage III NSCLC have been published, some showing equally remarkable 5-year patient survival of 22% to 29%[3,4] and becoming the standard of care in cooperative groups without even being properly controlled.[5] These promising results were subsequently not confirmed in randomized phase III trials.[6,7] The last decade has seen the advent of several novel radiation techniques that are likely to improve the local control by the administration of higher radiation doses to smaller volumes, allowing for lesser toxicity. There is a strong conviction that modern radiotherapy as part of a multimodality approach of patients with stage III disease will further improve outcome compared with the last decade. Opinions differ as to whether these advances, resulting in less irradiation of healthy tissue, should be confirmed by randomized trials or whether matched case-control studies will provide sufficient evidence.

The final answer can only be obtained by randomizing an adequate number of patients whose disease is down-staged to either modern radiotherapy or excellent thoracic surgery. Because of the sample size needed and the continuing improvements in radiotherapy delivery, it is unlikely that a trial of this size will ever be completed. Pending the results of these deliberations, the message to the community should be that even after a major response to induction therapy, patients with stage IIIA-N2 NSCLC should be primarily offered high-quality modern radiation and that surgery should be reserved for expert institutions and preferably as a part of a clinical trial.[8] All the rest is speculation.

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REFERENCES

1. Vansteenkiste J, Betticher D, Eberhardt W, De Leyn P. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small cell lung cancer (Editorial). *J Thor Oncol* 2007;2:684–685.
2. Van Meerbeeck JP, Kramer GWPM, Van Schil PEY, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. *J Natl Cancer Inst* 2007;99:442–450.

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3. Gandara DR, Chansky K, Albain KS, et al. Long-term survival with concurrent chemoradiation therapy followed by consolidation docetaxel in stage IIIB non-small-cell lung cancer: a phase II Southwest Oncology Group Study (S9504). *Clin Lung Cancer* 2006:116–121.
4. Uitterhoeve AL, Koolen MG, van Os RM, et al. Accelerated high-dose radiotherapy alone or combined with either concomitant or sequential chemotherapy; treatments of choice in patients with non-small cell lung cancer. *Radiat Oncol* 2007;2:27.
5. Kelly K, Chansky K, Gaspar LE, et al. Updated analysis of SWOG 0023: a randomized phase III trial of gefitinib versus placebo maintenance after definitive chemoradiation followed by docetaxel in patients with locally advanced stage III non-small cell lung cancer (Abstract). *J Clin Oncol* 2007;25: 7513.
6. Belderbos J, Uitterhoeve L, van Zandwijk N, et al. Randomised trial of sequential versus concurrent chemo-radiotherapy in patients with inoperable non-small cell lung cancer (EORTC 08972-22973). *Eur J Cancer* 2007;43:114–121.
7. Hanna NH, Neubauer M, Ansari R, et al. Phase III trial of cisplatin plus etoposide plus concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small cell lung cancer (Abstract). *J Clin Oncol* 2007;25: 7512.
8. Robinson LA, Ruckdeschel JC, Wagner H, Stevens CW. Treatment of non-small cell lung cancer-stage IIIA: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007;132:243–265.

